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Association between chlorhexidine gluconate concentrations and resistant bacterial bioburden on skin

Gita Nadimpalli, MD, MPH[1], **Lyndsay M. O'Hara, PhD, MPH**[1], **Surbhi Leekha, MBBS, MPH**[1], **David P. Calfee, MD, MS**[2], **Loren G. Miller, MD, MPH**[3], **Lisa Pineles, MA**[1], **Natalia Blanco, PhD, MPH**[1], **J. Kristie Johnson, PhD, D(ABMM)**[1,4], **Anthony D. Harris, MD, MPH**[1] **CDC Prevention Epicenters Program**

[1]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland [2]Division of Infectious Diseases, Weill Cornell Medicine, New York, New York [3]LA Biomedical Research Center at Harbor-UCLA Medical Center, Torrance, California [4]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland

Abstract

We studied the association between chlorhexidine gluconate (CHG) concentration on skin and resistant bacterial bioburden. CHG was almost always detected on the skin, and detection of methicillin-resistant *Staphylococcus aureus*, carbapenem-resistant *Enterobacteriaceae*, and vancomycin-resistant *Enterococcus* on skin sites was infrequent. However, we found no correlation between CHG concentration and bacterial bioburden.

Chlorhexidine gluconate (CHG) bathing is a widely implemented infection control measure.[1] In randomized trials and quasi-experimental studies, CHG has been demonstrated to decrease patient infection rates, frequency of healthcare worker contamination, and transmission of antibiotic-resistant bacteria.[2–4] CHG is believed to act by reducing contamination of the skin and, subsequently, the surrounding environment.[5] One study showed an inverse association between CHG concentration and gram-positive bacterial burden when CHG concentrations were >18.75 μg/mL[6]; however, this was a single-center study with only 20 patients. Despite increasing evidence suggesting the benefits of CHG bathing,[2–4] little research has been done to guide optimal CHG bathing practices by determining whether the CHG concentrations are associated with decreases in resistant bacterial bioburden in real-world settings.

The aim of our study was to examine the association between CHG concentrations and methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and vancomycin-resistant *Enterococcus* (VRE) bioburden on the skin. We hypothesized that the bioburden decreases as the CHG concentration on the skin increases. Additionally, we explored whether bacterial bioburden is affected by method and the time since the last CHG bath.

Author for correspondence: Dr Anthony Harris, aharris@epi.umaryland.edu.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

Methods

From May 2017 to August 2018, patients with MRSA, CRE, and VRE from 4 hospitals in the United States were enrolled as a part of a multicenter cohort study. All participants had a clinical or surveillance culture positive for 1 of these organisms within the previous 7 days. Intact skin was cultured to quantify bacterial bioburden using a sterile stencil at 2 sites: the antecubital fossa and the chest. CHG samples were collected from an adjacent area used to sample bacterial bioburden. At the time of patient enrollment, we recorded the method of CHG bathing (ie, 2% impregnated cloth or 4% CHG liquid soap) and time since the last CHG bath. To quantify bioburden, swabs were inoculated onto selective plates to count the colony-forming units per milliliter (CFU/mL) after serial dilution. A colorimetric, semiquantitative method was used to estimate CHG concentrations as previously described.[6–8]

Statistical analysis

Descriptive statistics for bioburden and CHG concentration were calculated. The CHG concentration was analyzed both as a continuous and a dichotomous variable (≤20 ppm vs >20 ppm) based on prior studies where a CHG concentration ≤18.75 μg/mL was considered inadequate to lower gram-positive bacteria.[6,8] The bacterial bioburden (x + 1) was log transformed, expressed in $\log_{10}$ CFU/mL, and analyzed as a continuous variable. All samples of MRSA, CRE, and VRE were analyzed in individual groups to study the relationships among the bacterial burden, CHG concentrations, time since last bath, and type of bath. The χ^2 test, Spearman's correlation, and linear regression were computed. Results were summarized as mean estimates and corresponding 95% confidence intervals.

Results

In total, 253 patients were enrolled in the study: 89 with MRSA (35%), 108 with CRE (42%), and 56 with VRE (22%). Moreover, 50 MRSA patients (56%) and 26 CRE patients (25%) were bathed with CHG cloths. All VRE patients were bathed with CHG liquid soap. The medians and interquartile ranges (IQRs) for CHG concentrations were as follows: MRSA,100 ppm (IQR, 30–200); CRE, 20 ppm (IQR, 0–100); and VRE, 10 ppm (IQR, 5–50). The median bacterial bioburdens were zero for MRSA, CRE, and VRE.

On the arm skin site, we detected MRSA in 17 patients (19%), CRE in 16 patients (15%), and VRE in 12 patients (21%). Detectable CHG levels were observed in 82 MRSA patients (93%), 81 CRE patients (79%), and 44 VRE patients (79%). We found a nonsignificant negative correlation between bioburden and CHG concentration for MRSA ($r_s = -0.11$; $P = .28$) and CRE ($r_s = -0.02$; $P = .82$), and a nonsignificant positive correlation was observed for VRE ($r_s = 0.15$; $P = .28$).

On the chest skin site, MRSA was detected in 25 patients (28%), CRE was detected in 18 patients (17%), and VRE was detected in 7 patients (13%). Detectable CHG levels were observed in 83 MRSA patients (95%), 78 CRE patients (72%), and 43 VRE patients (77%). We found a nonsignificant negative correlation between bioburden and CHG concentration

for MRSA (r_s = −0.16; P = .12) and nonsignificant positive correlations for CRE (r_s = 0.18; P = .06) and VRE (r_s = 0.24; P = .06).

We found no significant difference in bacterial bioburden when comparing CHG concentrations of >20 ppm with CHG concentrations ≤20 ppm (Table 1). On the arm skin site, we detected MRSA in 13 patients (18%), CRE in 6 patients (11%), and VRE in 6 patients (30%) with CHG concentrations >20 ppm, compared to MRSA in 4 patients (22%), CRE in 10 patients (19%), and VRE in 6 patients (17%) with CHG concentrations ≤20 ppm. On the chest skin site, we detected MRSA in 16 patients (24%), CRE in 10 patients (19%), and VRE in 5 patients (23%) among those with CHG concentrations >20 ppm, compared to MRSA in 9 patients (43%), CRE in 8 patients (14%), and VRE in 2 patients (6%) with CHG concentrations ≤20 ppm. The bioburden did not differ by the method of CHG bath. The mean estimates of bioburden on both skin sites did not show a significant decrease with an increase in CHG concentration from ≤20 ppm to >20 ppm and were not affected by the time since the last CHG bath (Table 2).

Discussion

In our study, CHG concentrations on the skin were high and the detection of MRSA, VRE, and CRE on 2 skin sites was infrequent. We did not find the hypothesized association between higher CHG levels and lower bacterial burden. Furthermore, our study suggests that CHG bathing reduces bacterial bioburden irrespective of the application method used.[9]

We did not find an inverse association between bacterial burden and CHG concentration when CHG concentration analyzed as a continuous variable[6,8] nor as a categorical variable ≤20 ppm or >20 ppm. Thus, CHG bathing may have a beneficial impact even at lower detectable concentrations. Our results are supported by Edmiston et al,[10] who found that the minimum inhibitory concentration of CHG for *Staphylococcus* skin isolates was 4.8 ppm, which is approximately the lower limit (5 ppm) of CHG detection in our assay. We used the same method to measure CHG levels as in previous studies[6–8]; however, the incongruent associations observed between the skin bioburden and CHG concentration, time since the last CHG bath, and CHG concentration raise the concern that the CHG assay for detection of CHG levels may not be reliable or that another CHG level monitoring device may be needed to acquire more accurate quantitative levels. Our findings are inconsistent with those presented by Popovich et al[6]; however, we studied different bacteria, and our sample size was notably larger.

A limitation of our study was that we quantified bioburden and recorded CHG concentrations only at 2 skin sites in comparison to previous studies that included 3–5 skin sites.[6–8] Moreover, with the high number of skin sites with no bacteria detected, our study was likely underpowered to assess the association between CHG concentration and bacterial bioburden.

In summary, our findings suggest that in hospitalized patients bathed with CHG, bacterial MRSA, CRE, and VRE bioburden on the skin is low, irrespective of CHG bathing method and the time since the last CHG bath. However, considering the inconsistent association

between levels of CHG on the skin and bacterial bioburden, additional research is needed. The daily frequency of CHG bathing has been arbitrarily chosen and standardized across all populations. It is plausible that CHG bathing frequency could be optimized for individual patient populations to augment the reduction of bacteria while minimizing side effects. To better implement these varying CHG bathing approaches, greater understanding of the association between CHG concentrations and resistant-bacterial bioburden is needed.

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Table 1.

Selected Characteristics of Patients at Each Skin Site by Bacterial Bioburden Detected for MRSA, CRE, and VRE

Variable	MRSA (n=89)			CRE (n=108)			VRE (n=56)		
	Detected No. (%)	Undetected No. (%)	*P* Value[a]	Detected No. (%)	Undetected No. (%)	*P* Value[a]	Detected No. (%)	Undetected No. (%)	*P* Value[a]
Arm sites									
CHG ≤20 ppm	4 (22.2)	14 (77.8)	.70	10 (18.5)	44 (81.5)	.27	6 (16.7)	30 (83.3)	.24
CHG >20 ppm	13 (18.3)	58 (81.7)		6 (11.1)	48 (88.9)		6 (30.0)	14 (70.0)	
4% CHG liquid soap	8 (20.5)	31 (71.5)	.76	12 (15.2)	67 (84.8)	.98	12 (21.4)	44 (78.6)	
2% CHG impregnate cloth	9 (18.0)	41 (82.0)		4 (15.4)	22 (84.6)		…[b]	…[b]	
Chest sites									
CHG ≤20 ppm	9 (42.9)	12 (57.1)	.08	8 (14.3)	48 (85.7)	0.49	2 (5.9)	32 (94.1)	.06
CHG >20 ppm	16 (23.5)	52 (76.5)		10 (19.2)	42 (80.8)		5 (22.7)	17 (77.2)	
4% CHG liquid soap	12 (30.7)	27 (69.2)	.62	13 (16.5)	66 (83.5)	0.74	7 (12.5)	49 (87.5)	
2% CHG impregnated cloth	13 (26.0)	37 (74.0)		5 (19.2)	21 (80.8)		…[b]	…[b]	

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; CRE, carbapenem-resistant *Enterobacteriaceae; VRE*, vancomycin resistant *Enterococcus*; CHG, chlorhexidine gluconate. Bathing with 4% CHG liquid was done using an entire 4 oz bottle of 4% CHG diluted in 4 l water.

[a] *P* value is for χ^2 test for categorical variable.

[b] No observations recorded.

Table 2.

Univariate Regression for Log Transformed Detectable Skin Bioburden for MRSA, CRE, and VRE Calculated Separately for Each Skin Site

	MRSA			CRE			VRE		
Variable	**Estimate**	**95% CI**	***P* Value**	**Estimate**	**95% CI**	***P* Value**	**Estimate**	**95% CI**	***P* Value**
Arm sites									
CHG concentration, ppm[a]	−0.31	(−1.7 to 1.1)	.65	−0.74	(−1.80 to 0.31)	.16	0.44	(−0.49 to 1.4)	.37
Time since last CHG bath, min	−0.01	(−0.03 to 0.01)	.08	0.01	(−0.01 to 0.01)	.83	−0.05	(−0.01 to 0.05)	.33
Chest sites									
CHG concentration, ppm[a]	−0.81	(−2.3 to 0.72)	.3	0.71	(−0.60 to 2.05)	.29	0.42	(−0.09 to 0.92)	.09
Time since last CHG bath, min[b]	−0.01	(−0.03 to 0.07)	.21	0.01	(−0.01 to 0.02)	.88	−0.04	(−0.01 to 0.02)	.22

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; CRE, carbapenem-resistant *Enterobacteriaceae*; VRE, vancomycin resistant *Enterococcus*; CHG, chlorhexidine gluconate; CI, confidence interval. At the time of patient enrollment, the most recent date and time of CHG bath prior to patient enrollment was recorded from the treating nurse and confirmed with the electronic medical record of the patient to estimate time in minutes since the last CHG bath.

[a]Estimate represents the calculated mean bioburden $\log_{10}$ CFU/mL for an increase in CHG concentration from ≤20 ppm to>20 ppm for arm and chest sites.

[b]Estimate represents the calculated mean bioburden $\log_{10}$ CFU/mL for every minute increase in the time since the last CHG bath for arm and chest sites.